

THE ETIOLOGY OF PELLAGRA: A CONSIDERATION OF VITAMIN DEFICIENCY.¹

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In a previous communication² it was suggested that the relation of corn to pellagra was analogous to the relation of rice to beriberi. The object of the present study was to determine the results of feeding chickens and pigeons on the offal of the corn mill (which is known as corn chops) after the development of symptoms produced by feeding deficient corn products. The second portion of the work has to do with the application of the information obtained by animal experimentation in the treatment of pellagra in man. Soon after starting the present work it became apparent that the milling and cooking of wheat products played an equally important part in the production of vitamin deficiency.

It had been shown by John M. Little³ that deficient wheat flour caused a form of polyneuritis in man which must be counted true beriberi. W. R. Ohler,⁴ prompted by a suggestion from Little, did extensive experimentation and produced the same type of polyneuritis by feeding chickens hominy as had been produced by deficient wheat. The result in both instances was the same as the type of polyneuritis produced with polished rice.

In 1914 Casimir Funk,⁵ who had introduced into medicine the term vitamin, and who had seen his theory regarding the causation of beriberi and its remedy verified, suggested that there was the same relationship between the milling of corn and pellagra as had been proved between the milling of rice and beriberi. There was no experimental or clinical evidence presented, however, and the suggestion did not receive the attention it deserved, though the advocates of a deficiency cause never lost sight of the possibility of such a solution. Funk pointed out the marked difference in the composition of corn and of the germ of corn. The fat content of the whole grain is 5 per cent., while the germ contains 30 per cent. The loss of fat was thought by him to be a good indicator of the loss of vitamin, as there was evidence to show that the fatty portion contained the vitamin. South African and American corn were both deficient, but the latter more so because of the higher degree of

¹ Presented at the meeting of the Association of American Physicians in Washington, May 10, 1916.

² Wood, E. J., Vitamin Solution of the Pellagra Problem, *Jour. Am. Med. Assn.*, May 16, 1916, vol. lxvi.

³ *Jour. Am. Med. Assn.*, 1912, lviii and 1914, lxi.

⁴ *Jour. Med. Research*, vol. xxxi (new series, vol. xxvi).

⁵ *Prophylaxe u. Therapie der Pellagra im Lichte der Vitaminlehre*, Munchen. med. Wehnschr., 1914.

milling. Funk was disposed to regard the mortality rate of the disease as an index of the degree of deficiency.

It had been shown in the beriberi work that phosphorus pentoxide was a reliable indicator of vitamin, though there was no direct connection between the two. The same value is attached to it in the present work. Sulphur determination is being introduced by us as an aid in determining vitamin, but the work has not progressed far enough to justify any definite conclusions as to its value in comparison with the phosphorus indicator. So far the results obtained show a striking similarity.

Viewing pellagra as a deficiency disease, and attributing the deficiency to the milling process or to some chemical change which brings about destruction of vitamin in the process of cooking, it is no difficult matter to reconcile and even harmonize many of the views of the early Spanish, Italian, and French pellagrologers. The vast amount of literature which has accumulated since the publication of Casal's⁶ original article has been very lifeless until recently. It now becomes reanimated by recent progress, and a careful study of this wealth of material is not only interesting, but of practical value, and we are filled with admiration at the keenness of the observation of those men who had so little opportunity for the accurate study of such a problem, and whose observations have stood so well the test of modern scientific advance. Sandwith⁷ states that as early as 1707 Pedro Casal wrote in Spanish that pellagra was due to insufficiency of diet. In the latter part of the eighteenth century Franzago declared that maize was unhealthy only because it was an insufficient food, but he would not say it was the sole cause. Later, Marzari⁸ claimed that the cause of the noxiousness of the corn was an insufficiency of gluten. Had there been a knowledge of Funk's theory of vitamin during that period in which corn was connected with pellagra in one way or another, the problem would probably have been solved long ago. The school of Lobroso had as a basis of its teachings a definite toxicity which may now be interpreted in terms of deficiency.

The germ of the corn lying at the hilus of the grain is poorly protected and subjected to the action of all injurious agencies both animal and vegetable. Damaged corn is always most affected in this part. Owing to the high fat content, the method of removing the germ before the grain was finally ground was introduced. This process was called "degermination." It is practised in many places and in many types of mill.⁹ The two products of this form of milling are granulated corn meal and corn chops. The latter is spoken of

⁶ *Historia natural y medica de el Principado de Asturias*. Abra posthuma del Doctor D. G. Casal, Medico de Su Magestad y su Protomedicin de Castilla, Madrid, 1762.

⁷ *Trans. Soc. Trop. Med. and Hyg.*, October, 1915.

⁸ *Essai Medico-politique*, 1810.

⁹ *Farmer's Bulletin*, 298, U. S. Dept. Agr.

as the offal of the corn mill and is sold as cattle food. In former times the grain was ground whole at the community water mill and there was no damage from the great heat which may be produced in rapid steam milling. This form of heat, however, is inconspicuous in comparison with the heating process which the grain often undergoes before reaching the mill.

The differences between corn chops and corn meal are given below:

	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Fiber, per cent.
Meal	9.2	1.9	74.4	1.0
Chops	9.0	7.0	70.0	9.0
Germ alone	21.7	29.6	44.7	
Endosperm	12.2	1.5	85.0	

Analysis of the various articles of food which were experimented with showed interesting variations in the P_2O_5 content. It was readily apparent that the cortex of the various grains, as has been formerly held, contained the bulk of phosphoric acid. It was also apparent that the amount was influenced by the degree of fineness of the product. Wheat middlings sifted in the laboratory with the removal of only the very smallest amount of bran showed a definite decrease in the phosphorus.

	P_2O_5 , per cent.
Corn chops	1.15
Water-ground meal (North Carolina)	0.78
Whole meal, steam milled (Virginia)	0.60
Highly milled meal (Ohio)	0.29
Steam-milled meal (North Carolina)	0.58
Wheat middlings (offal of mill)	0.98
Whole-wheat flour	0.50
Average wheat flour (bought in Wilmington, North Carolina)	0.14

The first important suggestion of a vitamin deficiency caused by the milling process was made by P. A. Nightingale¹⁰ in Rhodesia in 1912. He found that prisoners fed on highly milled meal developed a definite group of symptoms for which he coined the word "zeism," thinking it to be a new condition. There can be no doubt that this condition was acute pellagra, which has never been reported in medical literature except in the Southern States, in which it appeared in 1905. All references in European literature recognize pellagra only as a chronic process. Nightingale concluded that the use of highly milled meal had caused the disease, and substituted whole meal which was ground by hand in the jail. The result in his words was "immediate and magical."

Recent studies in polyneuritis gallinarum in its relation to beri-beri now become of great value in suggesting a line of investigation in pellagra. Goldberger¹¹ has emphasized the importance of viewing

¹⁰ Nightingale, P. A., Transvaal Med. Jour., 1912.

¹¹ Public Health Reports, June 24, September 11, October 23, 1914, Jour. Am. Med. Assn., October 10, 1914, and February 12, 1916, Public Health Reports, January 15, 1915.

pellagra in much the same light as beriberi, and we are indebted to him for the suggestion. It is not known that there is any connection between pellagra and beriberi, except that both diseases are probably deficiencies. Any experimental work in pellagra would, therefore, not be aided by a study of polyneuritis in fowl. The present work was undertaken to prove the fact that polyneuritis could be caused by meal made deficient in the milling process and cured by the portion of the grain removed in the production of the deficiency. Unexpected findings have thrown considerable light on the question, and have tended to suggest the possibility of a disease condition which seems to be due to a deficiency not so marked as to be sufficient to cause polyneuritis. It would seem that beriberi and pellagra, then, differ only in the degree of insufficiency.

The recent work of Voegtlin, Myers, and Sullivan¹² showed that vitamin was promptly destroyed by the use of soda and certain baking powders in the preparation of bread regardless of the original quality of the flour or meal. It was further shown that this could be prevented by the use of sour milk in conjunction with the alkali. Some baking powders contain enough tartaric acid to neutralize the sodium carbonate after the liberation of carbon dioxide. It is an interesting study to trace the introduction of this form of cooking and the appearance of pellagra, just as it is interesting to study the time connection between the introduction of highly milled meal and the disappearance of the old water mill which ground the corn *in toto*. In one community, at least, I have been able to show that the year which marked the abandonment of the old mill was the year of the appearance of the first cases of pellagra. Pellagra was unknown in the Confederate army, though lack of food was frequent; but there was no deprivation of the grains of any portion in the milling. There are broad areas in North Carolina in which pellagra has never occurred, though poverty and poor hygiene obtain in the fullest. These areas are separated from railroad travel, and home products are used through necessity. This is particularly true of the remote mountain counties. I have searched diligently through four such counties and have never been able to find the disease, nor could I learn of its occurrence from the physicians. But as the Piedmont section is reached and the people are able to procure manufactured products of every sort, the disease soon appears and reaches its high-point in the cotton-mill village, in which highly milled products are used almost exclusively and soda is added to every form of food to hasten the cooking (Voegtlin, Myers, and Sullivan).

Six pigeons were placed in a roomy cage outdoors with a floor to prevent the scratching of the earth. The best pigeon grit was abundantly supplied as well as plenty of fresh water. Whole corn was

¹² Public Health Reports, April 14, 1916.

broken in the laboratory and allowed in great abundance. No other food was given throughout the experiment. For four months there were no developments of disease, though it was evident that conditions were not best suited for growth and development. At one time it was noted that there was some droopiness, and investigation showed that the corn used at the time was of an inferior quality. From that time seed corn was used. This group were the controls.

In the second group of pigeons the food was corn meal with a P_2O_5 content of 0.58 per cent. After ten days it was noted that the pigeons had red legs in striking contrast to the controls, though of the same breed and age. In addition to the red legs there was marked droopiness and inactivity. After six weeks a more deficient meal with a P_2O_5 content of 0.29 per cent. was substituted. There was no change except increased redness of the legs. After these twelve weeks there had occurred only one death, and that from a cause having no bearing on the experiment. At this time it was decided to produce polyneuritis gallinarum if possible. Wellman and Bass¹³ as well as Ohler had produced polyneuritis in less than three weeks on a diet better than the one in use by us. The most deficient meal was made into bread, with the addition of soda. After a month of this feeding there was still no polyneuritis. During the experiment two squabs had been hatched from eggs laid after the experiment had been several weeks under way. These squabs did very well until the time for them to feed themselves. In a very few days polyneuritis developed. By the administration of corn chops there was prompt relief. It is a notable fact that these young pigeons were the only victims of polyneuritis, though the diet was such that it was to be expected that none of the animals would escape. The successful feeding of corn chops proved for corn what had already been proved for rice and wheat. By alcoholic extraction a substance was found in the corn chops which was equally as effective as the alcoholic extract of rice polishings had been in former experiments.

It appeared that continued feeding of a gradually increasing deficiency diet resulted in the acquiring of a peculiar kind of tolerance which may later be shown to explain some of the peculiarities of pellagra. After red-legged pigeons had been kept on the same food for several weeks it was impossible to produce polyneuritis with the most deficient diet, and the red-legged condition was just as promptly relieved by feeding corn chops as was polyneuritis. Only a few days were required for a return to normal, though it was found that the longer the red-legged condition had existed the longer the time required for a complete subsidence.

Chickens hatched on the same day were divided into two groups.

¹³ Am. Jour. Trop. Dis. and Prev. Med., 1913.

One group was fed deficient corn meal while the control group was fed corn chops. The food of the deficiency group contained 0.58 per cent. P_2O_5 in the beginning, which was later replaced by a meal with a 0.29 percentage. The red-legged condition did not occur, but the chickens did poorly. There was one case of polyneuritis gallinarum which did not respond to treatment because discovered late. The growth in every case was below normal and droopiness was quite marked. At the end of the experiment the chickens fed on corn chops had gained 8 per cent. more than those on deficient food.



FIG. 1.—Photographs of a Rhode Island cock, showing complete paralysis: a definite case of polyneuritis gallinarum caused by feeding cooked hominy.

Through the courtesy of a colleague we were given the opportunity to study polyneuritis gallinarum in a Rhode Island Red cock. The cause was cooked hominy. The photographs show the extreme degree of paralysis and the prompt recovery after the

administration of the extract of corn chops and a diet of the same food. This animal became neuritic by a change of diet which was not extreme, and at no time was there any confinement as in the experiments above recorded. The range was ample and the animal had abundant opportunity to supplement the hominy with other food. This suggests other factors not yet understood which play a part in deficiency conditions.

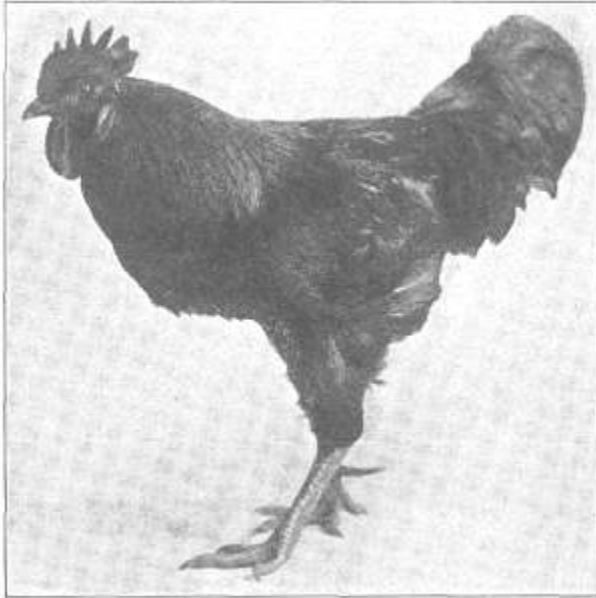


FIG. 2.—Photograph of the same cock forty-eight hours after feeding corn chops and the extract of corn chops. Improvement was immediate. Recovery was complete.

The red-legged condition was very definite and the cause was well established. The cure was equally simple. It would be beyond the scope of this work to attempt to show that the condition was analogous to pellagra as polyneuritis gallinarum is to beriberi. Suffice it to say that the observation was of the greatest help to us in our work, and by it we were able to determine very exactly the quality of the grain, for it was a very delicate indicator. We were disposed to regard polyneuritis as the result of a total deficiency and the red-legged condition as a partial deficiency. If this can be applied to pellagra it is readily understood why the coolie of the East has beriberi while in the South the deficiency disease is pellagra. The coolie eats one food and there is no chance for making up the deficiency with other foods. In the South there is always more than one food, and therefore the deficiency is made up in part at least.

Why it was impossible to produce polyneuritis gallinarum in the pigeons with the red-legged condition we cannot say. In several pellagrins we found polyneuritis which much resembled beriberi, though such a diagnosis was not ventured because of the frequency of the use of excessive dosage of arsenic in the disease. It is very probable that many cases of neuritis in pellagra have been caused in this way.

Feeling justified in the opinion that the portion of the grain removed in milling contained the vitamin, the lack of which caused pellagra, it was decided to feed pellagrins on exclusive diet of corn chops.

CASE I.—A white man, aged sixty-five years. Symmetrical erythema of the backs of the hands, stomatitis, diarrhea, prostration, and emaciation. For several months the diarrhea had been troublesome, and the number of stools varied from six to ten in twenty-four hours. On Wednesday morning he was placed on an exclusive diet of corn chops, but allowed a little butter. The corn chops was baked as bread without soda or baking powder, and was also made into a gruel. The patient was fed five times during the day. It was explained to him that the remedy was in the food and could not be successfully extracted. After forty-eight hours the relief was most striking: the diarrhea had ceased, the stomatitis was relieved, and desquamation was progressing rapidly. On Sunday he was discharged, with only the one complaint, constipation, to be considered. He was kept under observation for several weeks in the dispensary, and there occurred no recurrence.

CASE II.—A white man, aged fifty-six years. The backs of his hands were covered with a bullous erythema and the redness was intense. The first physician who saw him suspected a dangerous skin infection. The lesions were perfectly symmetrical. There was a complaint of stomatitis and diarrhea. In addition the patient was a diabetic. He was placed on a diet of corn chops, and at the end of four days the skin lesions were relieved and exfoliation was progressing rapidly, the diarrhea and all other symptoms had ceased. After a few days he was given the Allen fast and treated for the diabetes, with prompt disappearance of sugar. After three months there has occurred no recurrence of pellagra.

CASE III.—A well-conditioned white woman, aged twenty-two years. She had many peculiarities of diet, and as a result was suffering from pellagra of a typical type. The erythema covered the backs of her forearms, and there was a classic Casal collar. She complained of diarrhea and stomatitis. After four days of corn chops she was relieved of all symptoms, and at the end of a week desquamation was complete. After two weeks of this treatment she had gained eight pounds and felt better than in years. She was allowed other things besides the chops, but was required to eat the latter at least three times a day.

It was found that far-advanced cases were not relieved in this striking manner, though improvement often followed, and the treatment was well justified. After a time structural change takes place both in the intestinal tract and the nervous system, and no treatment can avail anything. This is equally true of other diseases for which there are specifics.

CASE IV.—A negro woman, aged about thirty years, was admitted to the hospital in a hopeless condition. She was far advanced in dementia. The bowels and bladder were being emptied in the bed, and the patient required an attendant constantly to keep her in bed. It was impossible to feed her except by the tube, which was used three times in the twenty-four hours. At each feeding a pint of milk and three eggs were given. There was some improvement, but it was not marked until four ounces of a gruel of wheat middlings was added. The intestinal condition improved promptly, and there would be periods of entire freedom from the diarrhea. The mental condition also improved, and the use of the tube was abandoned. The patient died rather suddenly from an unknown cause. In spite of the unfavorable termination there could be no doubt that the food caused improvement, and more markedly when the food containing grain cortex was added.

In all cases treated by the feeding method no drugs were used except an occasional placebo. It was soon learned that the corn chops to be effective must be freely milled. Just how this can be worked out practically remains to be demonstrated by some reliable dealer. Whatever the essential substance is there can be no doubt that it is very unstable, and apart from this, owing to the occurrence of rancidity, corn chops keeps very poorly. Some chemical process may be introduced to extract from the corn chops or the wheat middlings the essential substance. Our own efforts along this line, while proving that such a substance was present and could be extracted, were too expensive for practical purposes because of the great amount of alcohol necessary. Mr. G. F. Catlett was able to secure 65 c.c. of a watery substance from one kilo of corn chops by extracting with 8000 c.c. of 95 per cent. grain alcohol. The same general plan was followed as had been formerly used in the preparation of rice polish extract. The product made in our laboratory from corn chops was certainly as effective as rice polish in polyneuritis gallinarum when that condition was caused by defective corn. There is no reason to believe that it would not have been equally as effective if the polyneuritis had been caused by polished rice. Certainly in pellagra we were able to relieve the symptoms by the use of wheat middlings in one case and corn chops in others. This suggests that there probably is no specificity in the vitamin, but that all grains under discussion yield a certain amount, and that the only difference is one of richness.

While the bulk of our experimental work was confined to a con-

sideration of corn deficiency, we are entirely in accord with those observers who regard the wheat as a more frequent source of the deficiency in the South at this time. We were in a position to study the corn question, and were desirous of explaining in the beginning why polenta, the national dish of the Italian peasantry, caused pellagra. It can be readily accepted now that the toxicity of Lombroso was really a deficiency, and that the food forming almost the exclusive diet of the people under his observation was polenta. Polenta is a thick corn-meal mush, which was kept for days after its cooking, and which usually underwent fermentation. It has been shown that when corn is deficient the germ is usually the portion of the grain first and most seriously damaged regardless of the source of injury. Much of this Italian corn was badly damaged, and therefore was deficient because the vitamin had been destroyed in the germ. We will later study the result of fermentation on the vitamin content of polenta.

It is obvious that vitamin deficiency of the grain food may be replaced by an abundant protein diet of fresh lean meat, fresh milk, eggs, and various other expensive foods. It is also obvious that an infant may be protected from scurvy while on a faulty diet by giving such an antiscorbutic as orange juice. But is there justification for such a procedure? With the gradually increasing cost of foods of the vitamin supplying type, the poor whites of the South are no nearer their salvation from this great scourge. Lombroso once said that it would be equally as effective to advise his patient to be rich as to advise the diet needed, and if the patient were rich he would not have to be advised about the diet, for his natural desires would protect him from the disease. If decortication of grain and faulty methods of cooking cause the disease, the remedy is not beyond the reach of the poorest pellagrin. And this is our experience. It is, of course, granted that the high protein diet is most desirable, but the practical solution of the pellagra problem in the South calls for some other remedy. It can be easily shown that people live without meat, milk, eggs, and other expensive protein, and still do not suffer from pellagra. Our experience is that such people do not eat decorticated grains. We have also learned, as pointed out on a previous page, that the response from feeding pellagrins the decorticated portions of the grain is more prompt than when the diet is meat and eggs. It is to be hoped that the vitamin preparation of A. Seidel,¹⁴ which is prepared from brewer's yeast, using Lloyd's reagent, will be an inexpensive source of making up the deficit in the diet of the pellagra class. We have had no opportunity to test it in the treatment of the disease.

It would appear to us that pellagra is readily prevented; that the prevention does not require any increased cost of living; that the

¹⁴ Public Health Reports, 1916.

use of whole grains that have not undergone destructive changes and the avoidance of alkaline rising agents would entirely eradicate the disease.

It gives me pleasure to acknowledge my debt to Mr. G. F. Catlett, who by his sympathetic advice and aid in the chemical portion of this study has made it possible.

SALVARSAN IN THE TREATMENT OF DOUBLE INFECTIONS, TUBERCULOSIS, AND SYPHILIS.¹

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THE universal employment of the Wassermann reaction has revealed the striking frequency of an unknown or an unacknowledged syphilitic infection in patients with tuberculosis. The greater participation of careful internists in the problems of lues and the development of more recently devised tests have been responsible for showing that either as a result of their disease, or of its vigorous treatment, syphilitics exhibit an increased susceptibility to tuberculosis. Recent experience with the late lamented Paul Ehrlich's epoch-making drug, salvarsan, promises hope for the future in the treatment of patients afflicted with these combined infections, and very likely the diminution of syphilitics' susceptibility to the great white plague.

In ten years of prison service, Tedeschi² found that 70 per cent. of the cases of pulmonary tuberculosis had developed upon a luetic soil.

Among 346 tuberculous inmates of Boucicaut Hospital, 19 per cent. (64) gave a positive Wassermann reaction, although but 3 per cent. (10) acknowledged a previous luetic infection or showed any signs of it.³ Among 116 patients at Brompton Hospital with pulmonary tuberculosis selected at random by Inman,⁴ he found only 5 per cent. (6) positive. The admissions to a children's orthopedic hospital in Sweden⁵ during three years included 29 affections

¹ Read by title before the clinical section at the Eleventh Annual Meeting of the National Association for the Study and Prevention of Tuberculosis, held at Seattle June 14 to 16, 1915, but not completed in time for publication in the Transactions.

² Studium, Napoli, 1910, iii, 343, 377.

³ Bull. Acad. de méd., Paris, 1914, Series 3, lxxi, 596. (Abst.) Jour. Am. Med. Assn., Chicago, 1914, lxii, 1848.

⁴ Compt. rend. Soc. de biol., Paris, 1914, lxxvi, 254.

⁵ Norsk. Mag. f. Lægevidensk., Christiania, 1915, lxxvi, 557-696. (Abst.) Jour. Am. Med. Assn., 1915, lxiv, 2030.